1 419 681

PATENT SPECIFICATION

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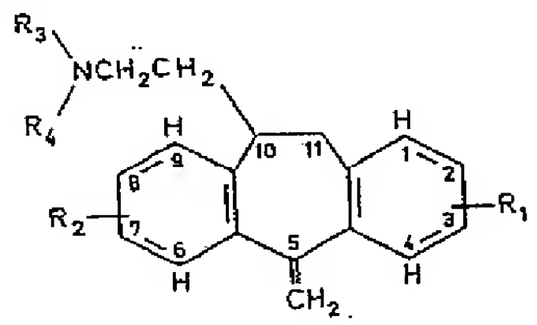
(54) AMINOALKYL-DIBENZOCYCLOHEPTENE DERIVATIVES

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel dibenzocycloheptene derivatives.

The invention provides compounds of formula I,

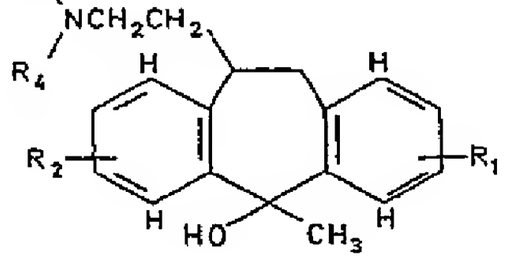


I

in which R_1 signifies hydrogen or fluorine
R_2 signifies hydrogen or fluorine, and
R_3 and R_4 independently signify methyl or ethyl.

The invention also provides a process for the production of compounds of formula I, which comprises

a) dehydrating a compound of formula II,



II

in which R_1 to R_4 are as defined above,

b) treating with sodium hydride, in the presence of an inert organic solvent, a compound of formula III,

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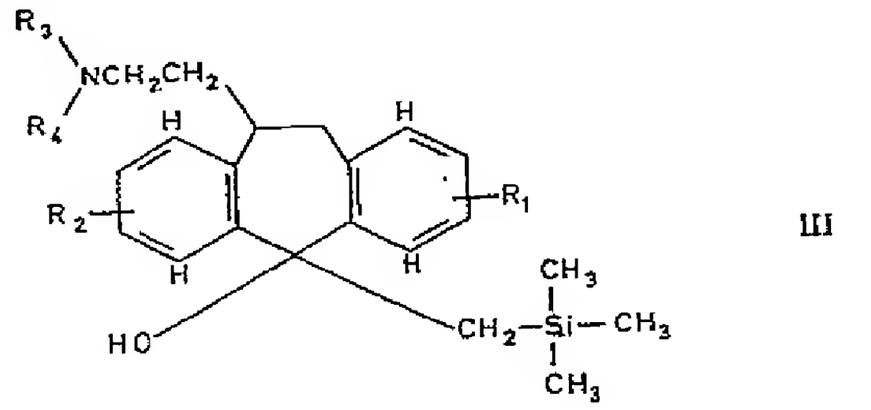
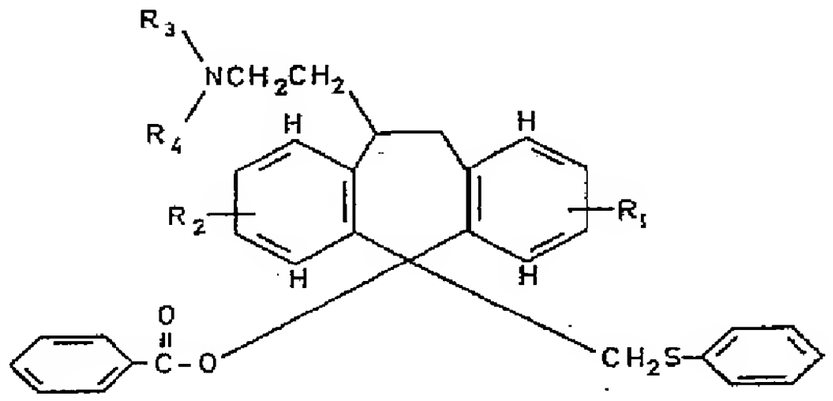


III

in which R_1 to R_4 are as defined above,

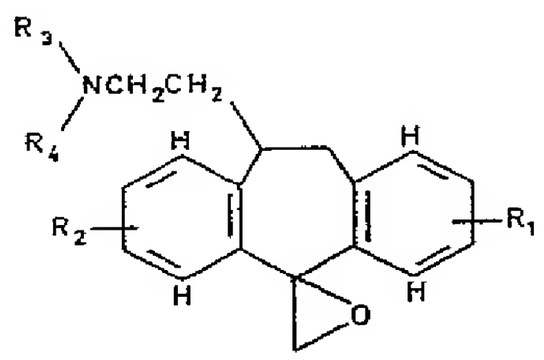
c) treating with lithium, in the presence of liquid ammonia and in the absence of oxygen, a compound of formula IV,



IV

in which R_1 to R_4 are as defined above.

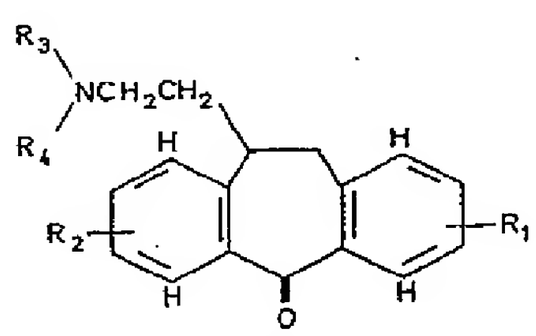
d) treating with triphenylphosphine a compound of formula V,



V

in which R_1 to R_4 are as defined above,

e) treating with methyltriphenylphosphonium bromide and sodium hydride, in the presence of dimethyl sulphoxide, a compound of formula VI,



VI

in which R_1 to R_4 are as defined above.

In process variant a), the dehydration is suitably carried out using a dehydrating agent such as a dilute or concentrated mineral acid, e.g. sulphuric acid or hydrochloric acid, 1M to 5M sulphuric acid being especially preferred, and it is preferred not to use nitric acid; iodine; phosphorus oxychloride; thionyl chloride; an alkyl- or aryl- sulphonyl chloride such as methanesulphonyl or benzenesulphonyl chloride; or a solid inorganic or Lewis acid such as potassium bisulphate, boric acid, aluminium oxide and silicon dioxide. When phosphorus oxychloride, thionyl chloride or an alkyl- or aryl- sulphonyl is used, it is preferred that the reaction be carried out in the presence of an acid binding agent such as a lower alkyl tertiary amine, e.g. triethylamine. When one of these dehydrating agents, of a solid inorganic or Lewis acid, is used, the reaction is preferably carried out in an inert organic solvent, especially a hydrocarbon such as benzene or

toluene. The reaction is suitably carried out at from 50°C to the reflux temperature of the reaction mixture, preferably at reflux. Reaction times are generally from 1 to 24 hours, under preferred conditions 1 to 4 hours.

In process variant b), the inert organic solvent is suitably a hydrocarbon such as hexane or heptane or an ether such as diethyl ether or tetrahydrofuran, especially the latter. The reaction temperature is not critical, but it is preferred to carry out the reaction at from −10 to +10°C, especially −5 to +5°C. Reaction times are generally from 2 to 10 hours, under preferred conditions 4 to 6 hours.

In process variant c), the reaction is suitably carried out under an inert atmosphere, e.g. under nitrogen, helium or argon or under ammonia gas. It is preferred to carry out the reaction in the presence of an inert organic solvent such as an ether, e.g. tetrahydrofuran or, especially, diethyl ether. The reaction temperature is not critical, but it is preferred to carry out the reaction at the reflux temperature of the system. Suitable reaction times are from 15 to 45 minutes, under preferred conditions 25 to 35 minutes.

In process variant d), the reaction may be carried out in an inert organic solvent such as an ether or a hydrocarbon. Suitable reaction temperatures are from 160 to 200°C, preferably 175 to 185°C. Suitable reaction times are from 3 to 8 hours, under preferred conditions 4 to 6 hours.

Process variant e) is preferably carried out at from 10 to 40°C, especially 20 to 30°C. Reaction times are generally from 30 minutes to 1½ hours.

The compounds of formula I may be isolated from the reaction mixture, and purified, in conventional manner.

The compounds of formula II may be prepared by a process which comprises reacting a compound of formula VI, defined above, with a compound of formula VII,

$$CH_3M \qquad \text{VII}$$

in which M signifies lithium, —MgCl, —MgBr or —MgI,
in an inert organic solvent and in the absence of oxygen, and hydrolysing the resulting adduct.

Suitable inert solvents are ethers such as diethyl ether or tetrahydrofuran and hydrocarbons such as benzene or toluene. The reaction is suitably carried out under an inert atmosphere such as nitrogen. When M is lithium, reaction temperatures are suitably from −20 to +25°C, preferably −5 to +5°C and reaction times are generally from 5 to 45 minutes, under preferred conditions 10 to 20 minutes. When the compound of formula VII is a Grignard reagent the preferred temperature is from 10 to 20°C and reaction times are generally from 1 to 6 hours, under preferred conditions 3 to 5 hours. Hydrolysis may be carried out in conventional manner, e.g. using water or an aqueous ammonium chloride solution.

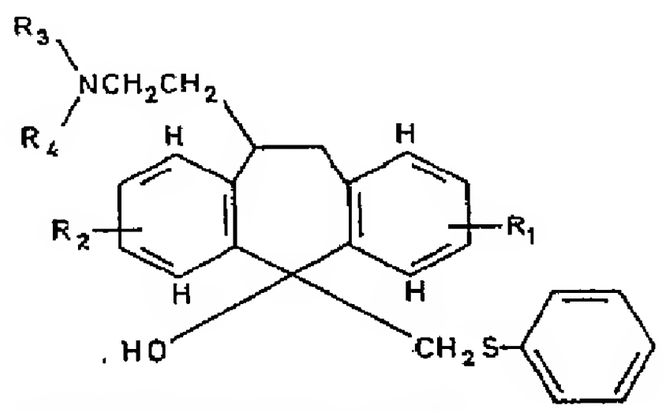
The compounds of formula III may be prepared by reacting a compound of formula VI with a Grignard reagent of formula VIII,

$$(CH_3)_3SiCH_2MgCl \qquad \text{VIII}$$

in the presence of an inert organic solvent, followed by hydrolysis in conventional manner of the resulting adduct.

Suitable inert organic solvents include tetrahydrofuran, heptane, hexane and, especially, diethylether. The reaction temperature is not critical, but is preferably the reflux temperature of the reaction mixture. Reaction times are generally about 2 to 10 hours, under preferred conditions 4 to 6 hours. Hydrolysis is preferably effected with aqueous ammonium chloride solution in conventional manner.

The compounds of formula IV may be prepared by reacting a compound of formula IX,



IX

in which R_1 to R_4 are as defined above,

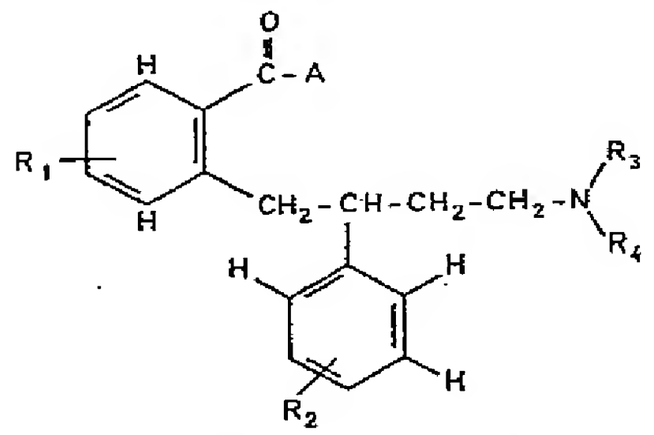
with an alkyl (C_{1-4}) lithium compound in liquid ammonia under an inert atmosphere, followed by reaction of the product with benzoyl chloride in the presence of an inert organic solvent.

The reaction with the alkyl lithium compound is suitably carried out at the reflux temperature of the system and under nitrogen and a suitable compound is butyllithium. Suitable inert organic solvents for the second step include tetrahydrofuran, heptane, hexane or especially, diethylether. The reaction temperature for the second step is conveniently from 10 to 40°C, especially from 20 to 30°C. The reaction time for the second step is generally about 1 to 5 hours, under preferred conditions 2 to 3 hours.

The compounds of formula IX may be prepared by reacting a compound of formula VI with phenylthiomethyllithium under an inert atmosphere, in the presence of an inert organic solvent. The reaction is suitably effected under nitrogen, helium or argon, and suitable inert organic solvents include diethylether, heptane, hexane and, especially, tetrahydrofuran. Suitable reaction temperatures are from 10 to 40°C, preferably from 20 to 30°C. Reaction times are generally from 15 to 30 hours, under preferred conditions 20 to 25 hours.

The compounds of formula V may be prepared by treating a compound of formula VI with trimethyloxosulphonium chloride, bromide, or, preferably, iodide, in admixture with sodium hydride and dimethyl sulphoxide. Suitable reaction temperatures are from 10 to 60°C, preferably 20 to 50°C. Reaction times are generally about 10 minutes to 2 hours, under preferred conditions 15 minutes to 1½ hours.

The compounds of formula VI may be prepared by a process comprising cyclising a compound of formula X,

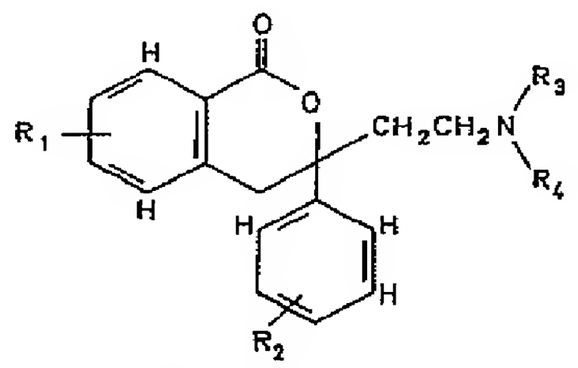


X

in which R_1 to R_4 are as defined above, and
A signifies hydroxyl, straight chain alkoxy of 1 to 4 carbon atoms or chlorine.

When A signifies hydroxyl or alkoxy, the cyclisation is preferably effected using a strong Lewis acid such as stannic tetrachloride, ferric chloride or titanium tetrachloride, or a strong mineral acid such as concentrated sulphuric acid or phosphoric or polyphosphoric acid. When a Lewis acid is used it is preferred to carry out the reaction in the presence of an inert organic solvent such as dichloromethane, carbon tetrachloride, carbon disulphide or nitrobenzene; a solvent is not necessary when a mineral acid is used, but solvents such as mentioned above may be used. When A signifies chlorine, the reaction is effected using a strong Lewis acid, preferably in the presence of a solvent, as mentioned above. Suitable reaction conditions generally are form 20 to 150°C, preferably from 100 to 120°C. Reaction times are generally about 2 to 10 hours, and under preferred conditions are about 3 to 5 hours.

Compounds of formula X in which A signifies hydroxyl may be prepared by reducing a compound of formula XI,



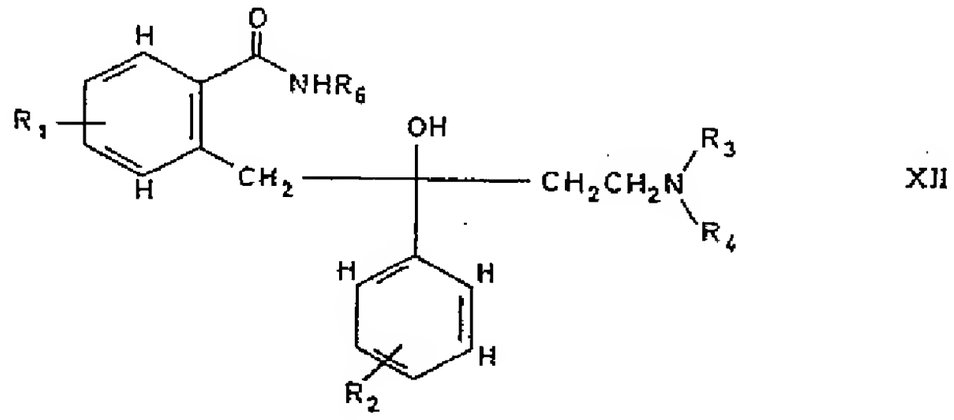
XI

in which R_1 to R_4 are as defined above,

Reduction methods particularly suitable are hydrogenation in the presence of a noble metal catalyst in the presence of an inert solvent and reduction by a zinc-ammonium hydroxide system. In the hydrogenation reaction, suitable catalysts are palladium, platinum and rhodium, and these may be neat or on a support such as charcoal. Suitable solvents are alkanols of 1 to 4 carbon atoms, such as ethanol, or acetic acid. Hydrogen pressures are conveniently about 35 to 100 psi, preferably 50 to 55 psi, and reaction temperatures are conveniently from 20 to 80°C, preferably 25 to 35°C. It is preferred to carry out the reaction in the presence of a catalytic amount of an aqueous mineral acid such as hydrochloric, sulphuric or perchloric acid. It is preferred to stop the reaction after absorption of one equivalent of hydrogen. The reduction using zinc-ammonium hydroxide is suitably carried out in the presence of a catalyst such as cupric sulphate, and is preferably carried out in the presence of an inert organic solvent such as a lower alkanol, e.g. methanol or, especially, ethanol. Suitable reaction temperatures are from 60 to 100°C, preferably 75 to 85°C. Reaction times are generally from about 24 to 48 hours, under preferred conditions 28 to 30 hours.

The compounds of formula X in which A signifies chlorine or alkoxy may be prepared from the acids in conventional manner.

The compounds of formula XI may be prepared by cyclising a compound of formula XII,



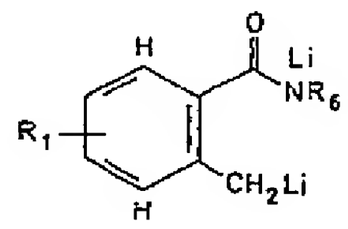
XII

in which R_1 to R_4 are as defined above, and

R_6 signifies alkyl of 1 to 4 carbon atoms.

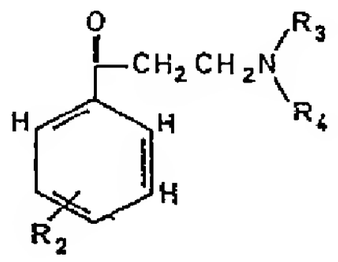
The cyclization is preferably effected by heating the compound of formula XII, conveniently at about 60 to 220°C, preferably at 140 to 160°C, for about 15 to 48 hours, under preferred conditions 20 to 28 hours. The compound of formula XII may be heated in an inert organic solvent such as tetrahydrofuran, or a hydrocarbon or halogenated hydrocarbon such as hexane, heptane, benzene, toluene or *o*-dichlorobenzene. It is preferred to heat the compound of formula XII under an inert atmosphere, e.g. under nitrogen.

The compounds of formula XII may be prepared by reacting a compound of formula XIII,



XIII

in which R_1 and R_6 are as defined above, and with a compound of formula XIV,



XIV

in which R_2, R_3 and R_4 are as defined above,

in an inert organic solvent and under an inert atmosphere, followed by hydrolysis of the reaction product in conventional manner.

Suitable solvents include diethyl ether, tetrahydrofuran, hexane, heptane benzene and mixtures thereof. The reaction is conveniently effected under nitrogen, suitably at a temperature from −30 to −15°C, preferably −25 to −20°C. Reaction times are generally about 1 to 3 hours. The compound of formula XIV is preferably added in solution in the inert solvent to a cold (−30 to −15°C) inert organic solvent solution of the compound of formula XIII. The hydrolysis is preferably effected with aqueous ammonium chloride solution in conventional manner, preferably at a temperature of from −15 to −5°C.

The compounds of formulae II, III, IV, V, VI, IX and X exist in acid addition salt form and may be prepared from the corresponding free bases and *vice versa* in conventional manner, and may be used in salt form in the various reactions described herein. The compounds of formulae II, III, IV, V, VI, IX, X, XI and XII may be isolated and purified using conventional techniques such as crystallization, evaporation of filtration. Certain of the compounds of formulae VII, VIII, XIII and XIV are known and may be prepared by methods described in the literature, and those compounds whose preparation is not specifically described may be prepared by known methods or methods analogous to known methods from known starting materials.

The compounds of formula I possess pharmacological activity. More particularly, they possess anti-depressant activity as indicated, e.g. by their activity in mice administered a compound intraperitoneally and tested according to the method basically as described by Spencer, P.S.J., Antagonism of Hypothermia in the Mouse by Antidepressant Drugs, pp. 194—204, Ed. S. Grattini and M.N.G. Dukes Excerpta Medica Foundation, 1967, and by their activity in cats tested for the compound's effect on 5-hydroxytryptophan and 1-tryptophan induced spinal monosynaptic reflex transmission, basically as described by Anderson, e.g., and Shibuya, T., The effects of 5-Hydroxytryptophan and 1-tryptophan on Spinal Synoptic Activity, pp. 352—360, J. of Pharm. and Exp. Therapeutics, Vol. 153, No. 2, 1966. The compounds are accordingly indicated for use as anti-depressants.

For such use, the indicated total daily dosage is in the range from 3 to 600 mg, conveniently administered 2 to 4 times a day in unit dosage form in which the amount of compound of formula I is in the range from 0.75 to 300 mg, or in sustained release form.

A particularly interesting compound of formula I is 10-(2-dimethylamino-ethyl)-10,11-dihydro-5-methylene-5H-dibenzo[a,d]cycloheptene.

For the above indicated use the compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such salt forms possess the same order of activity as the free base forms, and are readily prepared by reacting the free base with an appropriate acid, and accordingly are included within the scope of the invention. Suitable such salt forms include mineral acid salts such as the hydrochloride, sulphate and phosphate, and organic acid salts such as the succinate benzene-sulphonate and maleate.

The compounds of formula I exist as optical isomers. Such isomers may be resolved in conventional manner.

The invention also provides a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically acceptable acid addition salt thereof, in association with a pharmaceutically acceptable carrier or diluent. A suitable pharmaceutical form is a capsule containing the active compound.

A representative group of the compounds of formula I is that in which R_1 is in the 2-position, R_2 is in the 7-position and R_3 and R_4 are as defined above.

The compounds of formula VI (and a number of analogues thereof) and processes for their preparation, are described and claimed in our co-pending application number 28237/75 [Specification number 1,419,682].

The following Examples 3 to 7 and 10 illustrate the invention.

EXAMPLE 1.

2-(β-[2-Dimethylaminoethyl]-β-hydroxyphenethyl)-N-methylbenzamide (compound of formula XII)

To a flask equipped with a stirrer, dropping funnel, condenser and gas inlet tube maintained under a nitrogen atmosphere there is added at room temperature 40.4 g (0.28 mole) of *o*-methyl-N-methyl benzamide and 250 ml of anhydrous tetrahydrofuran. The reaction flask is immersed in an ice bath and cooled to an internal temperature of 5°C. Stirring is initiated and 360 ml of 1.6 M n-butyllithium

(0.616 mole) in hexane is added dropwise for about 1 hour maintaining the temperature below 8°C. The resulting red dilithio salt is stirred at 5°C for one additional hour and the reaction flask is then immersed in a dry-ice acetone bath and cooled to an internal temperature of –30°C. To the cold reaction mixture a solution of 49.7 g (0.28 mole) 3-dimethylaminopropiophenone in 140 ml of anhydrous tetrahydrofuran is added dropwise in *ca.* 45 minutes maintaining the temperature between –30°C and –20°C. The resulting reaction mixture is stirred at –25°C for 1 hour, allowed to warm to –10°C in *ca.* 1 hour, and then treated with 200 ml of saturated aqueous ammonium chloride while maintaining the temperature below 0°C. The resulting solid is filtered, washed thoroughly with water and recrystallized from methylene chloride-ether (1:1 v/v) to give 2-(β-[2-dimethylaminoethyl]-β-hydroxyphenethyl)-N-methylbenzamide; m.p. 139.5 to 140.5°C.

EXAMPLE 2.

3 - [2 - Dimethylaminoethyl] - 3,4 - dihydro - 3 - phenylisocoumarin (compound of formula XI)

To a flask equipped with a stirrer, condenser and gas inlet tube maintained under a nitrogen atmosphere there is added at room temperature 16.3 g (0.05 mole) of 2-(β-[2-dimethylaminoethyl]-β-hydroxyphenethyl)-N-methylbenzamide and 170 ml of *o*-dichlorobenzene. Stirring is initiated and the mixture is heated at reflux for 18 hours. The excess *o*-dichlorobenzene is then removed by distillation *in vacuo* and the resulting oil is crystallized from ether to give 3-[2-dimethylaminoethyl]-3,4-dihydro-3-phenylisocoumarin; m.p. 95.0—95.5°C.

EXAMPLE 3.

10-(2-Dimethylaminoethyl)-10,11-dihydro-5-methylene -5H-dibenzo[a,d] cycloheptane (process variant a))

a) 2-(β-[2-Dimethylaminoethyl]phenethyl)benzoic acid hydrochloride (compound of formula X)

A solution of 14.75 g (0.05 mole) of 3-(2-dimethylaminoethyl)-3,4-dihydro-3-phenylisocoumarin in 150 ml. ethanol containing 1 g 10% palladium on charcoal is hydrogenated at 50 psi and room temperature until one equivalent of hydrogen is absorbed. The mixture is filtered and evaporated to give the intermediate 2-[2-dimethylaminoethyl]phenethyl) benzoic acid hydrochloride; m.p. 152° to 154°C.

b) 10-(2-Dimethylaminoethyl)-10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5-one hydrochloride (compound of formula VI)

A mixture of 14.75 g (0.005 mole) of 2-(β-[2-dimethylaminoethyl] phenethyl)benzoic acid hydrochloride and 150 g of polyphosphoric acid is heated at 110°C for 6 hours allowed to cool and poured on to crushed ice with stirring. The resulting solution is cooled on ice and made basic by the addition of solid potassium hydroxide, and extracted with methylene chloride. The methylene chloride is washed with water, dried over anhydrous magnesium sulfate and evaporated *in vacuo*. The residue is dissolved in isopropanol, and treated with gaseous hydrogen chloride. The resulting precipitate is filtered and recrystallized from isopropanol to give the intermediate 10-(2-dimethylaminoethyl)-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one hydrochloride; m.p. 188—190°C.

Following the above procedure and using an equivalent amount of ferric chloride in place of polyphosphoric acid, there is obtained the identical product.

Similarly using ferric chloride and 2-(β-[2-dimethylaminoethyl]-phenethyl)benzoic acid chloride in place of 2-(β-[2-dimethylaminoethyl]phenethyl)benzoic acid hydrochloride, the identical product is again obtained.

Following the above detailed procedure but using 16.3 g of 2-(β-[2-dimethylaminoethyl]phenethyl)benzoic acid ethyl ester in place of 14.75 g of 2-(β-[2-dimethylaminoethyl]phenethyl)benzoic acid hydrochloride, there is again obtained the identical product.

c) 10-(2-Dimethylaminoethyl)-10,11-dihydro-5-methyl-5H-dibenzo [a,d]cyclohepten-5-ol (compound of formula II)

To a solution of 19.4 g (0.07 mole) of 10-(2-dimethylaminoethyl)-10,11-dihydro-5H-dibenzo [a,d] cyclohepten-5-one in 200 ml of diethylether, under nitrogen, cooled to –5°C, 70 ml of 1.5N methyllithium (0.105 mole) in diethylether is added dropwise with stirring, maintaining the temperature below 0°C and, 15

minutes after the addition is complete, the reaction is quenched by the addition of 50 ml of saturated ammonium chloride solution. The organic layer is separated, extracted with saturated sodium chloride solution, dried over anhydrous magnesium sulfate and evaporated. The crystalline residue is recrystallized from methylenechloride-methanol (1:1 v/v) to give the intermediate 10-(2-dimethylaminoethyl)-10,11-dihydro-5-methyl-5H-dibenzo [a,d]cyclohepten-5-ol; m.p. 161.5° to 162°C,.

Following the above procedure and using an equivalent amount of methylmagnesiumchloride in place of methyllithium at room temperature instead of 0°C for 3 hours instead of 15 minutes, the identical product is again obtained.

d) 10 - (2 - Dimethylaminoethyl) - 10,11 - dihydro - 5 - methylene - 5H - dibenzo [a,d]cycloheptene (compound of formula I)

A mixture of 8 g (0.027 mole) of 10-(2-dimethylaminoethyl)-10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5-ol and 250 ml 2M sulfuric acid is refluxed for 2 hours. The mixture is cooled in ice and made basic by the addition of solid potassium hydroxide. The mixture is extracted with methylene chloride. The methylene chloride is washed with water, dried over anhydrous magnesium sulfate and evaporated *in vacuo*. The oily residue is distilled at 140°C/0.5 mm and the distillate is dissolved in ethanol and treated with maleic acid. The precipitate is filtered and recrystallized from diethylether-ethanol 1:1 to give the product 10-(2-dimethylaminoethyl)-10,11-dihydro-5-methylene-5H-dibenzo[a,d]cycloheptene, in maleate salt form; m.p. 171—172°C.

Following the above procedure and using an equivalent amount of ferric chloride in place of sulfuric acid, there is obtained the identical product.

EXAMPLE 4.

a) 10 - (2 - Dimethylaminoethyl) - 10,11 - dihydro - 5 - trimethylsilylmethyl - 5H - dibenzo[a,d]cyclohepten - 5 - ol (compound of formula III)

A Grignard reagent is prepared by conventional techniques from 12.2 g (0.1 mole) of trimethylsilylmethyl chloride and 24.3 g of magnesium metal (0.1 g atom) and 200 ml of ether. The resulting solution is treated with 27.9 g (0.1 mole) of 10-(2-dimethylaminoethyl)-10,11-dihydro-5H-dibenzo[a—d]cyclohepten-5-one in 100 ml of ether. Stirring is initiated and the mixture is heated at reflux for 5 hours, then cooled in ice and hydrolyzed with 150 ml of saturated ammonium chloride. The layers are separated and the ether dried over anhydrous magnesium sulfate and evaporated to give 10-(2-dimethylaminoethyl)-10,11-dihydro-5-trimethylsilylmethyl-5H-dibenzo[a,d]cyclohepten-5-ol.

b) 10 - (2 - dimethylaminoethyl - 10,11 - dihydro - 5 - methylene - 5H - dibenzo[a,d] cyclohepten (compound of formula I, process b))

A suspension of 24 g (0.1 mole) of sodium hydride in 200 ml of tetrahydrofuran is cooled to 0°C and is added to a solution of 36.7 g (0.1 mole) of 10-(2-dimethylaminoethyl)-10,11-dihydro-5-trimethylsilylmethyl-5H-dibenzo[a,d]cyclohepten-5-ol in 200 ml of tetrahydrofuran while maintaining temperature at 0°C. After the addition is complete, the mixture is heated to reflux for 5 hours. The resultant mixture is cooled to 0°C and treated with 15 ml of methanol to remove any unreacted sodium hydride and the solvents are removed *in vacuo*. The oily residue is distilled at 140°C/0.5 mm and the distillate is dissolved in ethanol and treated with maleic acid. The precipitate is filtered and recrystallized from diethylether-ethanol (1:1 v/v), to give 10-(2-dimethylaminoethyl)-10,11-dihydro-5-methylene-5H-dibenzo [a,d]cycloheptene in maleate salt form; m.p. 171—172°C.

EXAMPLE 5.

a) 10 - (2 - Dimethylaminoethyl) - 10,11 - dihydro - 5 - phenylthiomethyl - 5H - dibenzo[a,d] cyclohepten - 5 - benzoate (compound of formula IV)

A solution of phenylthiomethyllithium (0.5 m) is prepared by reacting 6.22 g (0.05 mole) of thioanisole in 72 ml of dry tetrahydrofuran with 22.0 ml of 2.3M solution of phenyllithium for 15 hours at room temperature under nitrogen. A solution of 1.94 g (0.007 mole) of 10-(2-dimethylaminoethyl)-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one in 40 ml of tetrahydrofuran is added to a 42 ml (0.021 mole) portion of the phenylthiomethyllithium with ice-cooling. Stirring is initiated at room temperature for 24 hours. The resulting 10-(2-dimethylaminoethyl)-10,11-dihydro-5-phenylthiomethyl-5H-dibenzo[a,d]cycloheptene-5-ol is then poured on to a saturated salt solution and extracted with ether and the ether

solution dried over anhydrous magnesium sulfate. The ether solution is cooled in ice and treated with 4.5 ml of n-butyllithium in hexane (1.54 M solution 0.007 ice and 0.96 ml (0.008 mole) of benzoyl chloride in 10 ml ether is then added. The mixture is stirred for 3 hours at room temperature, diluted with ether and washed with water, saturated with sodium bicarbonate and then washed again with water. The ether is dried over anhydrous magnesium sulfate, filtered and evaporated and the residue purified to give 10-(2-dimethylaminoethyl)-10,11-dihydro-5-(phenylthiomethyl-5H-dibenzo[a,d]cyclohepten-5-benzoate.

b) 10 - (2 - Dimethylaminoethyl) - 10,11 - dihydro - 5 - methylene - 5H - dibenzo [a,d]cycloheptene (compound of formula I, process c))

To a refluxing solution of 0.28 g of lithium (0.4 mole) in 150 ml of liquid ammonia under nitrogen there is added a solution of 2.29 g of 10-(2-dimethylaminoethyl)-10,11-dihydro-5-phenylthiomethyl-5H - dibenzo[a,d]cyclohepten - 5 - benzoate (0.004 mole) in 50 ml of ether over about 30 minutes. Reflux is continued for an additional 30 minutes and then the mixture is hydrolyzed by the addition of ammonium chloride in small portions. The ammonia is evaporated while ether is added in small portions. The resulting mixture is added to water, the layers separated and the ether washed with 1N sodium hydroxide and water, dried over anhydrous magnesium sulfate, filtered and evaporated. The residue is dissolved in ethanol and treated with maleic acid. The resulting precipitate is filtered and recrystallized from diethylether-ethanol (1:1 v/v) to give 10-(2-dimethylaminoethyl)-10,11-dihydro-5-methylene-5H-dibenzo[a,d]cycloheptene; m.p. in maleate salt form 171—172°C.

EXAMPLE 6.

a) 10 - (2 - Dimethylaminoethyl) - 10,11 - dihydrospiro[dibenzo[a,d]cyclohepten-5,2' - oxirane (Compound of formula V)

A mixture of 27.6 g. of sodium hydride (0.12 mole) and 26.4 g of trimethyloxosulfonium iodide is treated slowly with 200 ml of dimethylsulfoxide. Stirring is initiated and a vigorous evolution of H_2 ensued, which stops after the addition was complete. The resulting mixture is then treated with 27.9 g (0.01 mole) of 10-(2-dimethylaminoethyl)-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one in 50 ml of dimethylsulfoxide. The reaction mixture is stirred for 15 minutes at room temperature and then at 50°C for 1 hour. The reaction mixture is then cooled and treated with a three fold excess of ice/water and extracted with ether. The ether is washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The residue is purified to give 10-(2-dimethylaminoethyl)-10,11-dihydrospiro[dibenzo]cyclohepten-5,2'-oxirane].

b) 10 - (2 - Dimethylaminoethyl) - 10,11 - dihydro - 5 - methylene - 5H-dibenzo-[a,d]cycloheptene (Compound of formula I, process d))

A mixture of 29.3 g of 10-(2-dimethylaminoethyl)-10,11-dihydrospiro-[dibenzo[a,d]cyclohepten-5,2'-oxirane] (0.1 mole) and 26.2 g of triphenylphosphine is heated at 180°C for 5 hours. The mixture is cooled and treated with water and ether. The layers are separated and the ether washed with water, dried over anhydrous magnesium sulphate, filtered and evaporated. The residue is distilled at 140°C/0.5 mm and the distillate is dissolved in ethanol and treated with maleic acid. The precipitate is filtered and recrystallized from diethylether-ethanol (1:1 v/v) to give 10-(2-dimethylaminoethyl)-10,11-dihydro-5-methylene-5H-dibenzo[a,d]cycloheptene maleate, m.p. 171—172°C.

EXAMPLE 7.

10 - (2 - Dimethylaminoethyl) - 10,11 - dihydro - 5 - methylene - 5H - dibenzo-[a,d]cycloheptene (process e))

A mixture of 2.3 g (0.1 mole) of sodium hydride and 50 ml dimethylsulfoxide are heated at 75—80°C until hydrogen evolution has ceased. The mixture is cooled in an ice-bath and 35.7 g (0.1 mole) of methyl triphenyl phosphonium bromide in 100 ml dimethyl sulfoxide is added. The resulting solution is stirred at room temperature for 10 minutes. Then 27.9 g (0.1 mole) of 10-(2-dimethylaminoethyl)-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one in 25 ml. of dimethyl sulfoxide is added and the mixture is stirred for one hour at room temperature then treated with a three fold excess of ice-water and extracted with ether. The ether extract is washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The residue is distilled at 140°C./0.5 mm. and the distillate is dissolved

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in ethanol and treated with maleic acid. The precipitate is filtered and recrystallized from diethylether-ethanol 1:1 to give 10-(2-dimethylaminoethyl)-10.11-dihydro-5-methylene-5H-bibenzo[a,d]cycloheptene maleate, m.p. 171—172°C.

EXAMPLE 8.

2-(β-[2-Dimethylaminoethyl]phenethyl)benzoic acid. (compound of formula X)

To a well stirred suspension of 45 g of zinc dust, 90 ml of concentrated ammonium hydroxide, 45 ml of water and 2 ml of cupric sulfate maintained at 80°C there is added 14.75 g (0.05 mole) of 3-(2-dimethylaminoethyl)-3,4-dihydro-3-phenylisocoumarin in 50 ml ethanol for about 30 minutes. The resulting mixture is heated at 85°C for 30 hours while a slow stream of ammonia is passed through. The mixture is filtered while under heat and the solids washed thoroughly with 100 ml. of hot ammonium hydroxide. The combined filtrates are cooled and carefully acidified with concentrated hydrochloric acid to give 2-(β-[2-dimethylaminoethyl]phenethyl)benzoic acid, m.p. as hydrochloride 152 to 154°C.

EXAMPLE 9.

2-(β-[2-dimethylaminoethyl]phenethyl)benzoic acid ethyl ester (Compound of formula X)

A solution of 29.7 g (0.1 mole) of 2-(β-[2-dimethylaminoethyl]phenethyl)-benzoic acid in 200 ml of ethanol is saturated with gaseous hydrogenchloride, and the resulting mixture is refluxed for 18 hours. The solvent is removed *in vacuo* and the residue is partitioned between ether and 2N sodium hydroxide. The ether extract is dried and evaporated *in vacuo* to give 2-(β-[2-dimethylaminoethyl]-phenethyl)benzoic acid ethyl ester.

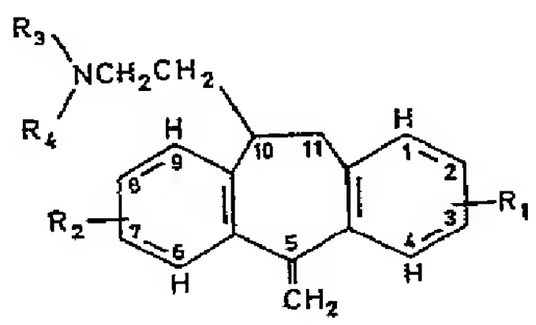
EXAMPLE 10.

10 - (2 - Dimethylaminoethyl)-10,11-dihydro-5-methylene-5H-dibenzo[a,d]cycloheptene

To a mixture of 5 g of 10-(2-dimethylaminoethyl)-10,11-dihydro-5-methylene-5H-dibenzo[a,d]cycloheptene maleate in 150 ml of methylene chloride there is added 50 ml of 2N-sodium hydroxide, the mixture is shaken, the methylene chloride is dried, filtered and evaporated *in vacuo* to give 10-(2-dimethylaminoethyl)-10,11-dihydro-5-methylene-5H-dibenzo[a,d]cycloheptene.

WHAT WE CLAIM IS:—

1. A process for the production of compound of formula I,

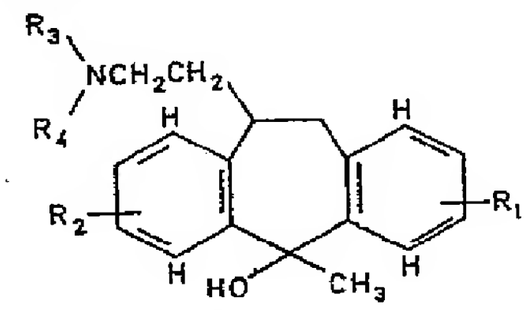


I

in which R_1 signifies hydrogen or fluorine
R_2 signifies hydrogen or fluorine, and
R_3 and R_4 independently signify methyl or ethyl,

which comprises

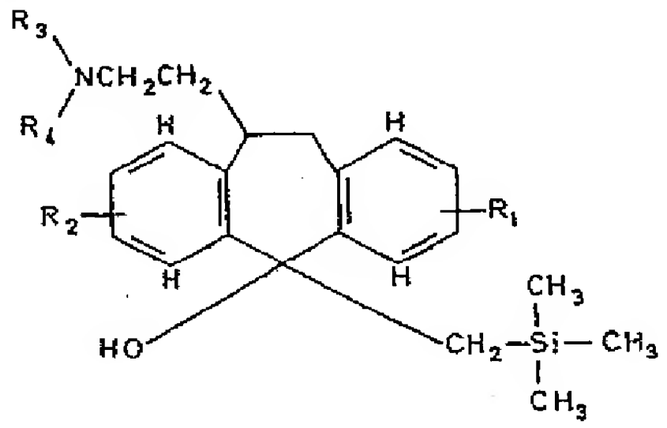
a) dehydrating a compound of formula II,



II

in which R_1 to R_4 are as defined above,

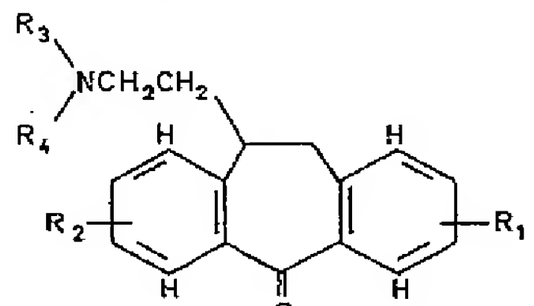
b) treating with sodium hydride, in the presence of an inert organic solvent, a compound of formula III,



III

in which R_1 to R_4 are as defined above,

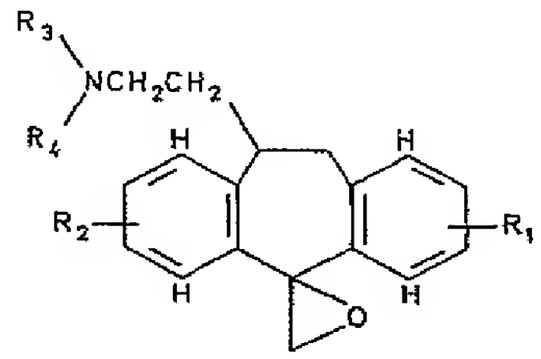
c) treating with lithium, in the presence of liquid ammonia and in the absence of oxygen, a compound of formula IV,



VI

in which R_1 to R_4 are as defined above.

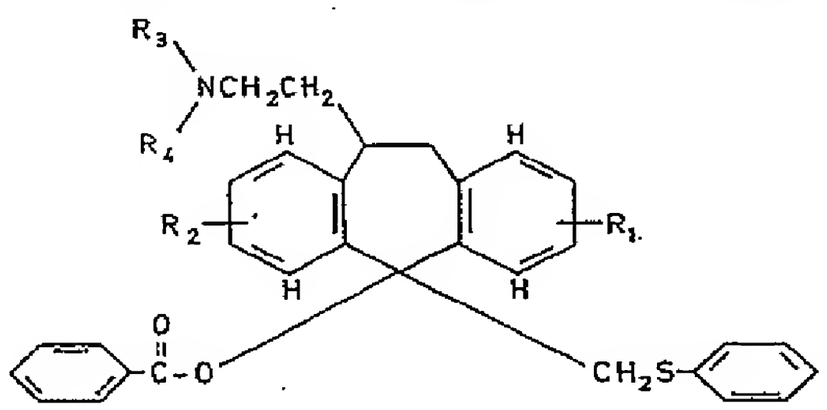
d) treating with triphenylphosphine a compound of formula V,



V

in which R_1 to R_4 are as defined above, or

e) treating with methyltriphenylphosphonium bromide and sodium hydride, in the presence of dimethyl sulphoxide, a compound of formula VI,



IV

in which R_1 to R_4 are as defined above.

2. A process for the production of a compound of formula I, stated in Claim 1, which comprises dehydrating a compound of formula II, stated in Claim 1.

3. A process for the production of a compound of formula I, stated in Claim 1, which comprises treating with sodium hydride, in the presence of an inert organic solvent, a compound of formula III, stated in Claim 1.

4. A process for the production of a compound of formula I, stated in Claim 1, which comprises treating with lithium, in the presence of liquid ammonia and in the absence of oxygen, a compound of formula IV, stated in Claim 1.

5. A process for the production of a compound of formula I, stated in Claim 1, which comprises treating with triphenylphosphine a compound of formula V, stated in Claim 1.

6. A process for the production of a compound of formula I, stated in Claim 1, which comprises treating with methyltriphenylphosphonium bromide and sodium hydride, in the presence of dimethyl sulphoxide, a compound of formula VI, stated in Claim 1.

7. A process according to Claim 2, in which the dehydration is effected using a dehydrating agent.

8. A process according to Claim 2 or 7, in which the dehydration is effected at a temperature of from 50°C to the reflux temperature of the reaction mixture.

9. A process according to Claim 3, in which the inert organic solvent is a hydrocarbon or an ether.

10. A process according to Claim 3 or 9, in which the reaction is effected at a temperature of from —10 to +10°C.

11. A process according to Claim 4, in which the reaction is effected in the presence of an inert organic solvent.

12. A process according to Claim 4 or 11, in which the reaction is effected at the reflux temperature of the system.

13. A process according to Claim 5, in which the reaction is effected in the presence of an inert organic solvent.

14. A process according to Claim 5 or 13, in which the reaction is effected at a temperature of from 160° to 200°C.

15. A process according to Claim 6, in which the reaction is effected at a tempreature of from 10° to 40°C.

16. A process according to Claim 1, substantially as hereinbefore described with reference to the Examples.

17. Compounds of formula I, whenever prepared by a process according to any preceding Claim.

18. Compounds of formula I, as defined in Claim 1.

19. Compounds of formula I, as defined in Claim 1, in which R_1 is in the 2-position and R_2 is in the 7-position.

20. 10-(2-dimethylaminoethyl)-10,11-dihydro-5-methylene-5H-dibenzo-[a,d]-cycloheptene.

21. A compound of formula I, according to any one of Claims 17 to 20, in acid addition salt form.

22. A pharmaceutical composition comprising a compound of formula I, in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutically acceptable carrier or diluent.

23. A pharmaceutical composition according to Claim 22, substantially as hereinbefore described.

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